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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,159	05/28/2003	Sean Farmer	19374-501	1649

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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
AFREMOVA, VERA	
ART UNIT	**PAPER NUMBER**
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/509,159	FARMER ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14, 15, 17-24, 34-38, 41-43, 49-51, 55-65, 67-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14, 15, 17-24, 34-38, 41-43, 49-51, 55-65, 67-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 14, 15, 17-24, 34-38, 41-43, 49-51, 55-65, 67-69 are pending and under examination.

Claim Rejections - 35 USC § 112

Written description

Claims 14, 15, 17-24, 34-38, 41-43, 49-51, 55-65, 67-69 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims are drawn to a method of *in vivo* treating yeast and fungal infections by topically applying *Bacillus coagulans* strain ATCC 31284 to skin or to mucous membrane.

The as-filed specification fails to describe a method of *in vivo* treating yeast and fungal infections by topically applying *Bacillus coagulans* strain ATCC 31284 to skin or to mucous membrane.

The as-filed specification only describes compositions with the cells belonging to some generic representative of the species of *Bacillus coagulans* (page 27-28; formulation 1 and 4) as intended for control of fungal and yeast infections (examples 4, 5 and 7 at pages 29, 31 and 33). However, as related to the *in vivo* administration the as-filed specification only suggests some generic doses and/or generic protocols of topical administration of probiotic compositions with generic representatives of *Bacillus coagulans* to some unidentified generic patients. As related to the actual methods for inhibiting yeast or fungal infections including vaginal infections the

specification only discloses the ***in vitro*** assays (example 1, pages 24-27) of antimicrobial activity of *Bacillus coagulans* ATCC 31284 (page 12, line 7) towards infections belonging to *Tichophyton* species and *Candida* species. The protocol of the *in vitro* assays is based on measuring inhibition zones on agar plates. No animal cells including skin or mucous membrane cells are involved in the *in vitro* assays as disclosed. No animals were used as *in vivo* model systems for inhibiting or treating yeast and/or fungal infections including vaginal infections. The specification does not disclose how to extrapolate data obtained from the *in vitro* antimicrobial studies on the agar plates as obtained with the stain ATCC 31284 towards development of effective *in vivo* therapeutic treatment including human therapeutic treatment in order to commensurate in scope with the claimed invention.

Given this lack of written description of the *in vivo* use of the claimed strain ATCC 31284, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention as drawn to *in vivo* application of strain ATCC 31284.

Enablement

Claims 14-24, 34-43 and 49-69 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The as-filed specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation. Factors to be considered in determining

whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Nature of instant invention is directed to the compositions with the *Bacillus coagulans* probiotic cells to control microbial infections.

The breadth of the claims is directed to a method for inhibiting yeast and/or fungal infections including vaginal infections by applying topically to skin or to mucous membrane a probiotic composition with specific *Bacillus coagulans* strain ATCC 31284. Some claims are further drawn to inhibiting *Tichophyton* and *Candida* infections on skin and or mucous membrane.

The as-filed specification discloses compositions with the cells belonging to generic representatives of the species of *Bacillus coagulans* (page 27-28; formulation 1 and 4) as intended to control fungal and yeasts infections (examples 4, 5 and 7 at pages 29, 31 and 33). But the as-filed specification only suggests some generic doses and/or generic protocols of topical administration of generic *Bacillus coagulans*-containing probiotic compositions to some unidentified generic patients.

As related to the actual methods for inhibiting yeast or fungal infections including vaginal infections the specification only discloses the ***in vitro*** assays (example 1, pages 24-27) of antimicrobial activity of *Bacillus coagulans* ATCC 31284 (page 12, line 7) towards infections belonging to *Tichophyton* species and *Candida* species. The protocol of the *in vitro* assays is based on measuring inhibition zones on agar plates. No animal cells including skin or mucous membrane cells are involved in the *in vitro* assays as disclosed. No animals were used as *in vivo* model systems for inhibiting or treating yeast and/or fungal infections including vaginal infections.

Thus, the specification does not adequately demonstrates that the claimed strain ATCC 31284 is capable to effectively inhibit yeast and/or fungal infections on skin or on mucous membrane in an in vivo environment because neither animal cells nor live animals were used in experiments for inhibiting yeast and/or fungal infections. Therefore, the specification does not and cannot adequately teach how to effectively treat yeast and/or fungal infections including vaginal infections because no animal cells and/or no live animals were used to demonstrate inhibition of infections by probiotic compositions with the claimed strain.

The state of the prior art in teaches that selection of probiotic strains is based on several considerations. For example: see page 312, col. 2 of the reference by O'Sullivan et al. "Probiotic bacteria: myth or reality?". Trends in Food Science and Technology. 1992. 31:309-314. In particular, the cited reference O'Sullivan et al. teaches that the selected strain must be recognized as generally safe and it should be a normal inhabitant of the site of application and/or be capable of surviving and growing in the site of application. The presently claimed strain ATCC 31284 appears to be a generally safe bacterial strain since it has been used for making food products

such as Japanese youguronatto (US 4,110,477). However, the source of isolation of the strain ATCC 31284 is unknown and, further, for the fact of being a suggested food component the claimed stain ATCC 31284 does not appear to be a normal inhabitant of skin or mucous membrane such as vaginal surface. Furthermore, neither instant specification nor the prior art provides information about capability of the strain 31284 to survive and to grow in the site of intended application such as on skin surface or on vaginal mucous membrane.

The cited reference O'Sullivan et al. also teaches that adherence to body surfaces is an important prerequisite for *in vivo* survival and growth of the probiotic strain (page 312, last par.) and that even demonstration of adherence *in vitro* does not guarantee that adherence and subsequent colonization would occur *in vivo* as the strain must overcome the host defense mechanism to provide for a competitive advantage over infectious microbes (page 313, par. bridging col. 1 and col. 2). The instant specification does not contain scientific evidence about adherence of the claimed *Bacillus coagulans* strain ATCC 31284 to animal cells including epithelial or to animal body surfaces either in vitro or in vivo. Moreover, the applicants' related patent US 6,461, 607 teaches that vegetative cells of *Bacillus coagulans* representatives do not adhere to epithelial cells (col. 23, lines 57-59). Thus, there is a reasonable believe that vegetative cells of the claimed *Bacillus coagulans* strain ATCC 31284 might not possess capability to adhere and to growth on epithelial surfaces including skin and vaginal mucous membranes. Therefore, the claimed strain ATCC 31284 would not be able to compete with infectious yeasts and fungi on skin surface and on vaginal surface in order to enable the scope of instant claims.

With respect to the claims drawn to application of the strain ATCC 31284 in form of spores, it is also noted that even if spores might be capable to survive in the *in vivo* environment,

upon germination the vegetative cells of the strain ATCC 31284, even if grown form spores in the *in vivo* environment, still would not be able adhere and to growth on epithelial surfaces in order to compete with infectious yeasts and fungi. Therefore, the claimed strain ATCC 31284 when used in form of spores would not be able to compete with infectious yeasts and fungi on skin and on vaginal surface in order to enable the scope of instant claims.

The prior art also teaches that attachment to epithelial cells is very host specific which means in practical terms that a strain which is suitable for development as a pig probiotic may not be active in other animals, for example: see page 374, lines 22-24 of the reference by Fuller "Probiotics in man and animals". Journal of Applied Bacteriology. 1989, 66: 365-378. Thus, the claimed invention as drawn to administration of the strain 31284 to some generic patients raises to uncertainly about animal applications as a whole including human applications of the strain 31284 in the lack of scientific evidence.

With regard to unpredictability of the claimed methods as drawn to inhibiting vaginal infection, Seligman (British Journal of Obstetrics and Gynaecology. October, 1995. Vol. 102, pages 763-764) teaches that the studies of the use of probiotics or of bacilli in the treatment of vaginitis have almost all been limited, uncontrolled and have given variable results (page 763, col. 2, par. 4, lines 1-4). Thus, the state of the art provides no reasonable expectation of success.

Therefore, in view of the art teaching, in view of unpredictability in selecting and using probiotic strains and also considering total lack of working examples in the specification demonstrating adherence of the clamed strain 31284 to animal cells and its capability to survive and growth on skin and vaginal surface, the claimed method fails to comply with the enablement requirement.

Accordingly, undue experimentation is necessary to determine protocols of administrating strain 31284 to patients suffering from yeast and fungal infections for inhibiting these infections. Without sufficient guidance the methods as claimed are unpredictable and the experimentation left to those skilled in the art is unnecessarily, improperly, extensive and undue.

Response to Arguments

Applicant's arguments filed 3/28/2007 have been fully considered but they are not persuasive.

With regard to the claim rejection under 112-1 (written description) applicants argue that the instant claims meet the written description requirement because they have either "express, or inherent, or implicit support for the claim as a whole" on some selected pages and, in particular, on page 12, lines 6-9, the specification states, "The results described herein were obtained with B. coagulans Hammer obtained from the American Type Culture Collection (ATCC# 31284) which was grown as described herein and stored in lyophilized aliquots at -20°C." However, the instant claims are directed to *in vivo* application of the strain ATCC 31284 but the written disclosure describes only ***in vitro*** assays of antimicrobial activity of *Bacillus coagulans* ATCC 31284 (page 12, line 7 and pages 24-26) towards infections belonging to *Tichophyton* species and *Candida* species. The protocol of the *in vitro* assays is based on measuring inhibition zones on agar plates. No animal cells including skin or mucous membrane cells are involved in the *in vitro* assays as disclosed. The as-field specification does not contain any description about possible adherence of the claimed *Bacillus coagulans* strain ATCC 31284 to animal cells including epithelial or to animal body surfaces either in vitro or in vivo. No *in vivo* models or

systems for inhibiting or treating yeast and/or fungal infections including vaginal infections with any *Bacillus coagulans* including *Bacillus coagulans* ATCC 31284 are described in the as-field specification. Given this lack of written description of the *in vivo* therapeutic effects of topical applications of *Bacillus coagulans* including the claimed strain ATCC 31284, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention as drawn to *in vivo* topical application of the strain ATCC 31284.

With regard to the claim rejection under 112-1 (enablement), applicants argue that rigorous or exact correlation between in vitro and in vivo systems are not required and that if the art is such that a model is recognized as correlating to a specific condition, then the model should be accepted as a correlation unless the Examiner has evidence that the model does not correlate. First, it is uncertain as argued whether in vitro antimicrobial activity of Bacillus coagulans on agar plates would correlate with competitive exclusion of pathogens by Bacillus coagulans grown on infected animal epithelial cells. Furthermore, there is an evidence that vegetative cells of *Bacillus coagulans* representatives do not adhere to epithelial cells as disclosed in the applicants' related patent US 6,461, 607 (col. 23, lines 57-59). The adherence to body surfaces is an important prerequisite for *in vivo* survival and growth of the probiotic strain (O'Sullivan et al. at page 312, last par.). Moreover, even demonstration of adherence *in vitro* does not guarantee that adherence and subsequent colonization would occur *in vivo* as the strain must overcome the host defense mechanism to provide for a competitive advantage over infectious microbes (O'Sullivan et al. at page 313, par. bridging col. 1 and col. 2). Therefore, in view of the art

teaching, in view of unpredictability in selecting and using probiotic strains and also considering total lack of working examples in the specification demonstrating adherence of the clamed strain 31284 to animal cells and its capability to survive and growth on skin and vaginal surface, the claimed method fails to comply with the enablement requirement.

No claims are allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1657

June 22, 2007

V. Afremova

VERA AFREMOVA

PRIMARY EXAMINER